Approaches in Chemoprevention of Oral Cancer by Vitamin A and Green Tea

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ABSTRACT

Oral cancer is one of the most common cancers which is the 6th most prevalent cancer in the world. It has been established that incidence of cancer increases with age. The diagnosis of oral cancer is easily possible by a visit of the dentistry. According to various studies, oral cancer is preventable and numerous epidemiological studies have approved the positive effects of daily consumption of vegetables in reducing the risk of oral cancer. Chemical prevention is the use of drugs for prevention and suppression of natural or precancerous cells from transforming into cancerous cells. Vitamin A and green tea have antioxidant properties. Various studies have confirmed the effects of 13-cis retinoic acid in preventing dysplasia and leukoplakia of oral cells, but other studies have shown that the long-term use of 13-cis retinoic acid as a preventative chemical has side effects and also, probability of recurrence is very high. Green tea is another widely used substance in the prevention of malignancy. In various studies, the anticancer effects of green tea and particularly its impact on the prevention of oral cancer has been demonstrated. Polyphenols found in green tea are known as inhibiting factors for the processes involved in growth and metastasis of cancerous cells. High acceptance of green tea and also the fact that it leaves no side effects makes it considered as a suitable substance for chemopreventive procedures against cancer and particularly oral cancer. In this article we compared the effect of the vitamin A and green tea's effects on oral cancer prevention and care.

Key words: Chemoprevention, Oral cancer, 13-cis retinoic acid, Green tea, Polyphenol and Vitamin A.

INTRODUCTION

According to the progressive various cancers including colon, breast, uterus and prostate in recent years, oral cancer has also been ranked as the most common cancers that accounts in 6th Category (Jemal et al., 2007; Parkin et al., 2005). Every year 274,000 people in the world were diagnosed with oral cancer (Parkin et al., 2005; Kupferman et al., 2006). This cancer according to gender in industrialized countries is 3rd most common cancer in men and 4th in women. The incidence of this cancer increases directly with ageing (Johnson, 2001). According to the research conducted about this cancer, everyday one person dies because of oral cancer (Jemal et al., 2007; Jemal et al., 2008). Despite of all the medical advances that have been made in the treatment of oral cancer; the 5-year survival rate of oral cancer is still below 50%, which that in compare with other cancers, it was not not improved (Jemal et al., 2007).

Oral cancer is associated with secondary tumors with a prevalence of 20 to 30 percent (Fuller et al., 2007). Detection of oral cancer in people who are visually observed by the dentist only needs 90 sec to go but, unfortunately due to lack of medical staff and lack of attention by the dentists in checking for cancer; the disease detected in 3 or 4th grade; actually lymph node metastases stage (American Dental Association, 2001). From the multistage epidemiological studies that were done about oral cancer, presented results reveals that oral cancer is a preventable cancer (Lee et al., 2011). Oral cancer can prevent by early identification and the best way of prevention is to using the chemical

prevention (Papadimitrakopoulou et al., 2009). Several epidemiological studies confirms the positive preventive effects of regular and adequate intake of foods of plant origin on the development of various cancers; including fruit, vegetables, oilseeds, nuts and tea (Doll et al., 1981; Beliveau et al., 2007); and another epidemiologic studies proves that, consumption of fruits and vegetables in smokers was less and this is why they do not receive adequate antioxidants (Dallongeville et al., 1998; Wei et al., 2001; Philips et al., 2000).

In the body, there are important antioxidants that organize a system as micro-nutrition form of antioxidants (Evans et al., 2001). The function of these substances is neutralization of free radicals, and this leading to prevent the occurrence of oxidative reactions (Helen et al., 2006). Chemoprevention is a theory that was presented by Sporn et al. (1976). Chemoprevention is use of natural medicines or chemicals to prevent suppress and expel neoplastic cells that are susceptible for cancerous (Lee et al., 2011). These materials prevents form creating cancerous cells by preventing from DNA damage or remove materials that damages DNA during the cell cycle of injured cells (Alizadeh et al., 2014). Antioxidants such as vitamin A and its derivatives, which also have used in clinical application, found mainly in fruits and vegetables. Several epidemiological studies have shown that low serum levels of antioxidants have a direct relation with increasing risk for the incidence of cancer; especially cancers of the mouth and airways (Mezzetti et al., 1995; Lykkesfeldt et al., 2000; Ross et al., 1995; Stryker et al., 1988; Chainian-Wu, 2002).

The chemicals used for chemoprevention procedure must have features such as (1) Less toxic or non-toxic, (2) High efficacy at various points, (3) Can intake orally, (4) Known mechanism of action, (5) Low cost and (6) Be accepted by the patient (Rajamanickam et al., 2008). Prevention and specially chemoprevention of cancer is an important strategy to save the lives of patients and reduce mortality that caused by probably surgeries in involved patients. Several studies were done about receiving antioxidants and the effects of these substances on the human body and animals; Also several studies were done on the intake of antioxidants in smokers and non-smoker and like that, but in this field, there is few histological studies were done in discussion of the effects of antioxidants on the related tissues but in this article, two of the most important materials in medical chemoprevention (Green tea and vitamin A) were introduced and a comparison were accomplish between the effects of each material on the chemical prevention of oral cancer and cancer progression.

MATHERIALS AND METHODS

Study Design

This study is a review of literature that was performed from 2014 to 2016. A total of 100 articles in subject of cancer and especially oral cancer chemoprevention from Scopus, Google Scholar and PubMed with no publishing time limitation were selected. At the end 88 articles was selected. Searched key words were: Oral Cancer, Cancer Prevention, Chemoprevention, Vitamin A and Green Tea. Articles published time varies from 1939 to 2013.

RESULTS

Vitamin A

There is a similarity between bronchial lesions found in carcinogen-treated animal's squamous metaplasia and the histological changes affecting the bronchial epithelia of humans or animals who has deficient in vitamin A. In this state, restoration to a normal histological state occurs after vitamin A repletion, which in experimental models has also been shown to confer protection against pro-carcinogens (Bogos et al., 2008). Several studies have confirmed the effect of the 13-cis retinoic acid (13-cRA) in preventing oral cells dysplasia and leukoplakia affected by the transition (Bogos et al., 2008). Similar studies have shown that certain doses of vitamin A are effective on cancerous cells and in the study of Papadimitrakopoulou et al. (2009), the consumption level of 20 mg/ml have positive effect on 100% of non-smokers and 92% of former-smokers and 8.5% of smokers in the preventing of development of oral cancer (Papadimitrakopoulou et al., 2009); and also in a similar study, in the case of 13-cRA chemical prevention of oral cancer it was observed that 13-cRA in preventing from oral cancer, but it have harmful effects on smokers and had the opposite very preventive effect in non-smoker, so the percentage of response to treatment with 13-cRA was equal to 48.1% (Lippman et al., 2001; Mayne et al., 2005).

Vitamin A is an effective antioxidant material, but other studies have shown that retinoids leave toxic effects after treatment and after discontinuation; the risk of cancer recurrence is very high (Bogos et al., 2008). From the toxicity basis, this material shows the toxicity grades 2 and upper that 13-cRA toxicity that is indicated nearly 53%. According to other studies in the field of chemical prevention of head and neck this grade of toxicity is confirmed (Khuri et al., 2006). Most of these findings demonstrate that low-dose of long-term using of 13-cRA does not have preventive effect on oral cancer and in a study of 1190 patients with head and neck cancers, low-doses of 13-cRA was ineffective in preventing of secondary cancers (Khuri et al., 2006).

Green Tea

Green tea derivate from the plant named "Camellia Sineasis" and after water, this is one of the most
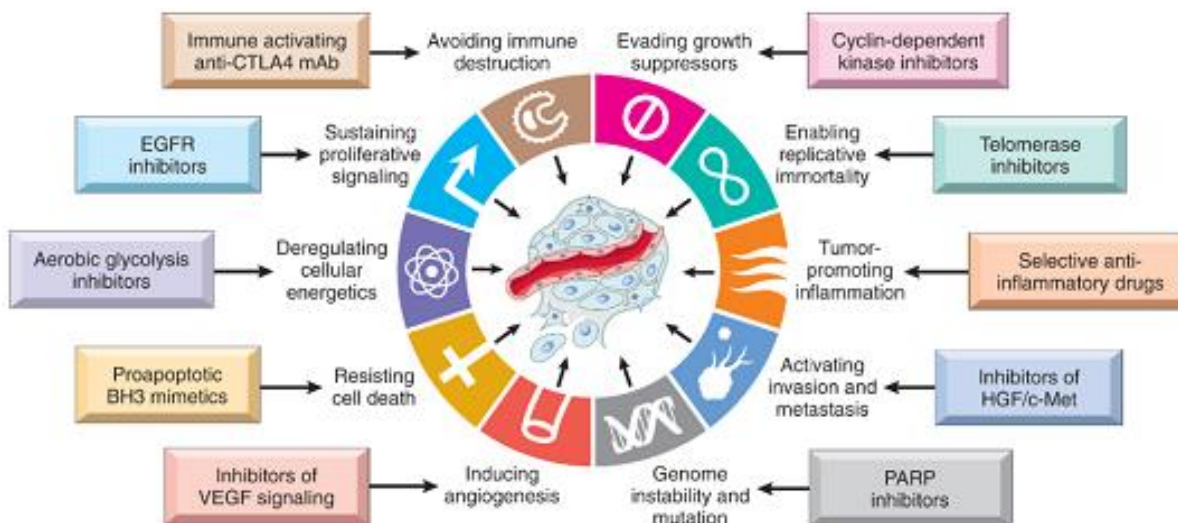
Figure 1. Therapeutic targeting of hallmarks of cancer (From Hanahan D, Weiberg RA; The hallmarks of cancer: The next generation.

consumed beverages in the world (Beltz et al., 2006). This material has attracted a lot of attention because of having positive effects on human health. Green tea contains polyphenols, glycosides, leucoanthocyanins, and phenol acid (Balentine et al., 1997); witch the polyphenols constituting 36% of the fresh green tea leaf dry weight (Graham et al., 1992). Several studies have shown that polyphenols have important effects on human health and certainly have inhibitive effect on cancer cells progression in the skin, lungs, oral cavity, liver, pancreas, ovaries and breast (Ahmad et al., 1999; Jankun et al., 1997; Su et al., 2002; Yang, 2001; Zhang et al., 2004). Four major polyphenols of green tea is: (1) Epicatechin (EC), (2) Epigallocatechin (EGC), (3) Epicatechin-3-gallate (ECG) and (4) Epigallocatechin-3-gallate (EGCG); this polyphenols amounts in the fresh green tea leaf are composing 1 to 3, 3 to 6, 3 to 6, and 7 to 13%, respectively, of the dry weight (Graham et al., 1992).

In the feature studies, chemopreventive effects of various polyphenols on cancers and specifically EGCG have been demonstrated (Adhami et al., 2003; Hsu et al., 2002; Ju et al., 2005; Lambert et al., 2005; Masuda et al., 2002; Masuda et al., 2003). A cup of green tea contains 200 $_{mg}$ of EGCG (Yang et al., 2002). Preventive effects of green tea on cancer due to the extensive research done in the field of cell culture and biopsies that prepared from animals were confirmed (Chung et al., 2003). Polyphenols found in green tea has been identified as inhibitor of the processes involved in cancer cell growth and metastasis (Gu et al., 2008). Important clinical considerations emerge from the principles present in the foregoing discussion of the hallmarks of cancer. These hallmarks provide a road map for the development of new therapeutic agents for the treatment of cancer as shown in Figure 1 (Kumar et al., 2013). The implications on the

anticancer activity are reported to be on important enzymes like urokinase (Jankun et al., 1997), ornithine decarboxylase, NADPH-cytochrome P_{450} reductase, protein kinase C, steroid 5-alpha reductase (Liao et al., 1995), tumor necrosis factor expression (Suganuma et al., 1999) and nitric oxide synthase (Lin et al., 1998). Anticancer effects occur through pathways of anti-angiogenesis (Cao et al., 2002).

Polyphenols in green tea have a major impact on the control of cell growth in cancer cells to prevent metastasis and survival of cancer cells by affecting the amount of DNA and RNA and their protein (Beltz et al., 2006). A recent study shows that EGCG binds to a group of proteins, including Laminin, Vimentin, Fas and Insulin-like growth factor (IGF) receptor. It is also an indirect effect on epidermal growth factor receptor (EGFR) and signal transducers and activators of transcription (STATs) and activator protein-1 (AP1). EGCG is also a potent inhibitor of nuclear factor kappa-light-chain-enhancer (NF-kB) of activated B cells pathways (Sazuka et al., 1998; Hayakawa et al., 2001; Suzuki et al., 2001; Ermakova et al., 2005; Shim et al., 2008; Li et al., 2007; Ermakova et al., 2006; Hastak et al., 2005; Amin et al., 2007). Green tea polyphenols can induce cell cycle arrest or apoptosis through activation of p53 or the p21 and Bax protein and its related proteins (Hastak et al., 2003). Studies show that EGCG cause apoptosis through activation of a group of target gene expression of a subset of p53-dependent apoptosis, include p73. These genes include: p21, cyclin G1, MDM2 (mouse double minute 2), WIF1 and PIG1. Target genes that are negatively regulated by EFCG include: Bcl2, Bcl-xl, cyclin D1, matrix metalloproteinases (MMPs), and vascular endothelial growth factor (VEGF). VEGF identified as a potential target for chemopreventive action. Studies in

this area have shown that green tea polyphenols have the ability to block angiogenesis in breast cancer cells by inhibiting the expression of VEGF and MMP9, which act through STAT3 pathway (Sartippour et al., 2001; Leong et al., 2009). Evidence suggests that treatment with EGCG prevents phosphorylation of EGFR tyrosine kinase in head and neck cancers (Masuda et al., 2002). EGCG induces internalization and ubiquitin mediated degradation of EGFR ultimately undermining EGFR signaling. EGCG has been extensively studied for its chemopreventive and therapeutic potential (Yang et al., 2000). Several studies have shown the inhibitive effects of EGCG on tyrosine kinase receptors, including HER2, HER3, insulin like growth factor-1 receptor (IGF-1R) and VEGFR. Laminin receptors that organize many intracellular signaling pathways; known as a potent receptor for EGCG binding (Zhang et al., 2008; Masuda et al., 2003; Sah et al., 2004; Syed et al., 2007).

DISCUSSION

Clinical Trials in Oral Cancer Prevention by Vitamin A

Recent clinical trials that were done in the oral cancer chemoprevention and based their strategy on the use of substances such as vitamin A and its derivatives; adenoviruses, pharmacological agents and natural compounds for cancer chemotherapy. The first study of retinoids for preventing the chemical had been used by Sporn et al. (1976) that conducted chemoprevention into the mainstream of the research on cancer (Sporn et al., 1976). Prominent studies have shown that treatment with high-dose 13-cRA can reduce the damage caused by cancer by 67% in patients treated with 13-cRA that is significant in comparison with the control group that was 10%. These studies have shown that vitamin A derivatives can be prevented dysplasia (Hong et al., 1986). Evidences demonstrates that treatment with high dose 13-cRA and at the end of treatment, taking continues lower dose of 13-cRA is better than beta-carotene usage in the confronting with precancerous tissues (Lippman et al., 1993). Another phase III clinical trial that used high-dose of 13-cRA, showed apparent reduction in tumor growth and the treatment takes 1 year to 3 years of using the chemopreventive agent (Hong et al., 1990).

In another study which used the high-dose of 13-cRA, vitamin E, beta-interferon showed that the composition of these materials has very high impact on inhabitation and delay of the head and neck cancers and the cancers of relevant secondary tumors; there is also a similar effect in preventing tumor recurrence is after the cancer treatment (Shin et al., 2001). High doses of 13-cRA acts as a successful treatment against precancerous oral tissue but long-term uses of the drug have a high degree of toxicity. To reduce the toxicity of 13-cRA in the long term usages,

early use of low-dose suggested but was not successful in preventing of progression of head and neck cancers (Papadimitrakopoulou et al., 1997; Lippman et al., 2001; Khuri et al., 2006).

Clinical Trials in Oral Cancer Prevention by Green Tea

Regular consumption of green tea, 3 to 5 cups a day provides the minimum amount of 250 mg per day of the body's certain catechines (Boehm et al., 2009). Results in the reduction of the use of green tea as chemopreventive agents in patients prone to oral cancer are shown (Li et al., 1999; Tsao et al., 2009). In a long-term study that done by Imai and et al. (1997) have been done of 8552 Japanese that used at least 10 cups of green tea daily (each cup 120 ml) significantly reduced the incidence of cancer (Imai et al., 1997). In a pilot study that the amount 2000 to 2500 mg per day of green tea in the drinking water for 4 weeks were consumed by smokers showed that during the period of green tea, the damage of cigarette smoke on the DNA of the germ cells that were in the phase S was reduced and also significantly inhabitation of the cancer cells growth were observed, and most cells were in G1 phase of cell cycle. Additionally in this study, markers of apoptosis were also reached to minimum (Schwartz et al., 2005).

In another clinical trial of green tea in oral precancerous tissues was done using a double-blind, randomized trial, placebo -controlled in patients with oral leukoplakia by a blend of green tea capsules and ointment of green tea has been used as much as totally 760 mg and placebo patients were treated with topical glycerin. The group treated with green tea during the period of 6 months, was 37.9% responsible to the treatment. These results are consistent with a decrease in EGFR positive cells in the treated patients (Li et al., 1999). To estimate the maximum tolerated dose of green tea for the body, a phase I trial was conducted. Results shows a the total of catechines = 26.9, EGCG = 13.2, EGC = 8.3, ECG = 3.3, EC = 2.2, caffeine contents = 6.8 which comes with a green tea extract (GTE) ideal dose of either once or third for minimum 4 weeks up to a maximum of 6 months. Toxic effects in high doses usage of green tea leads to tremors, cough, constipation and headache. These symptoms are due to the presence of caffeine in the GTE. This study shows that the direct addition of GTEs to different tissues can help to improve the local concentrations of the active constituents in these lesions. Pathologic results also shows a significant decrease in the number and total volume of the silver-stained nuclear organization centers and the proliferation cell nuclear antigen in oral mucosa in patients treated with green tea in a comparison with the control group (Tsao et al., 2009). In other study promising results observed in the evaluation of patients with high risk oral premalignant lesion whom were selected randomly and used three

different doses of GTE (500,750,1000 $_{mg/m^2}$) for at least 12 weeks. Control patients also received 3 random daily doses of placebo for at least 12 weeks. After 12 weeks, biopsy tissues were examined and the key biomarkers in the target tissues were measured. Result showed a response by 58.5% at high doses of 750 and 1000 and 36.4% at the dose of 500; and in the comparison, the placebo group shown 18.2% of responsibility to placebo treatment. According to the results, it appears that mentioned doses (500, 750, 1000 $_{mg/m^2}$), have high-impact on oral premalignant lesions. Also, results showed a significant decrease in the expression VGEF that is trusted by previous study.

This study shows down-regulation of stromal VGEF and cyclin D1 in the tissues of patients with a positive response to treatment with GTE and show up-regulation in nonresponsive patients. By the observation, it found that the GTE inhibits the growth of oral premalignant lesions and their second tumor causes by blocking antigen stimulation in that lesions. This study not only supported the use of GTE in chemoprevention of oral premalignant lesions but also use of relevant biomarker in clinical trials to monitor the response. At the molecular level, the only way to identify the mechanism of action of chemopreventive agents depends on the responsiveness and sensitivity through the use of relevant biomarkers. This was identified that the green tea is a natural substance and is an acceptable chemopreventive agent for its non-toxic chemopreventive capacity (Leong et al., 2009; Masuda et al., 2002). A phase I trial that compared the minimum toxic dose and minimum tolerant dose endpoint, found that using green tea has not any toxicity and have high and safe tolerant dose endpoint. Molecular markers can effectively aid in the determination biological activity in a chemopreventive settings (Khafif et al., 1998). Green tea has also been used along with curcumin; another popular natural compound. Previous studies have shown synergistic growth inhibitory effects of curcumin in the prevention of head and neck cancer (Khafif et al., 1998). Topical curcumin and receiving oral GTE, totally have effective anti-tumor effects in the cancers caused by 7, 12, dimethylbenzanthracene *in vivo* (Li et al., 2002).

CONCLUSION

So in a conclusion, due to vitamin A toxicity in long-term use, type of effect on cancer cells progression, the continued use of the substance to prevent cancer because of the recurrence of the cancer after vitamin A withdrawal; it is preferred to looking for a cancer preventive agent that have no complications like this. Among the many natural substances, green tea's polyphenols, especially EGCG is known as a chemopreventive agent with high rate of treatment response and no recurrence of cancer even after withdrawal. Studies in this area are confirmed green tea's effectiveness in responding to chemoprevention of oral cancer.

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